UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MISSOURI
EASTERN DIVISION
(St. Louis)

IN RE: CELEXA AND LEXAPRO PRODUCTS LIABILITY LITIGATION	:	**MDL DOCKET NO. 1736**
	:	**ALL CASES**
	:	
	:	**Judge Rodney W. Sippel**
	:	

MEMORANDUM IN SUPPORT OF DEFENDANTS' MOTION TO EXCLUDE TESTIMONY OF PLAINTIFFFS' EXPERT DAVID HEALY, MD

I. INTRODUCTION

Forest asks the Court to exclude the unreliable and irrelevant testimony of plaintiffs' expert, David Healy, M.D. Dr. Healy's opinions do not satisfy the requirements for admissibility of expert testimony. His opinions will not assist the trier of fact in understanding the evidence or determining a fact in issue because they are not based on generally accepted scientific principles or methodology.

Dr. Healy attempted to offer nearly identical opinions ten years ago using the same flawed methodology. After exhaustive review and analysis, including the appointment of independent experts, a federal district court excluded the testimony of Dr. Healy and the Tenth Circuit Court of Appeals affirmed.

In the ten years since Dr. Healy was excluded, the issue whether CELEXA® and LEXAPRO®, and SSRI antidepressants as a class of drugs, cause people to commit suicide has been extensively researched and studied. Multiple epidemiological studies, including a meta-analysis by the FDA involving nearly 100,000 adult clinical trial participants, failed to demonstrate an association between CELEXA, LEXAPRO (or any other SSRI antidepressant)

and suicide or suicidality in patients 25-years of age or older.[1] Indeed, today the FDA requires all SSRI manufacturers to state in their package inserts that "[s]hort-terms studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older."[2] And other research supports a protective effect from suicidal acts for all adults. (*See* p. 40 *infra* and FN 43.)

Although every decedent but one remaining in this MDL was 25-years of age or older when they were prescribed CELEXA or LEXAPRO, Dr. Healy fails to address the volume of epidemiologic studies (all peer-reviewed) that contradict his opinions. Instead, he simply ignores them. Accordingly, as he was ten years ago in a similar case, Dr. Healy should be excluded here.

II. DR. HEALY'S OPINIONS ARE THE SAME AS THOSE PROPERLY REJECTED TEN YEARS AGO

A physician/psychiatrist from Wales, Dr. Healy is plaintiffs' sole expert on the issue of general causation.[3] He was identified to Forest, and his report was served, on December 2, 2011 (Schaefer Dec., Exhibit 4, Report of David Healy, M.D., hereinafter "Healy Report.") Dr. Healy was deposed on March 12, 2012, in Los Angeles, California, while he was in the United States promoting his most recent book, PHARMAGEDDON, and his latest website, www.risk.org. (Schaefer Dec., Exhibit 5, Deposition of David Healy, M.D. (hereinafter "Healy Dep.") pp. 17-18.)

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1 Mark Stone, et al., "Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration," BMJ 2009; 339: b2880 ("Stone Paper"). (Copy attached to Declaration of Jeffrey R. Schaefer Filed in Support of Defendants' Motion to Exclude Testimony of Plaintiffs' Expert, David Healy, M.D. ("Schaefer Dec.") as Exhibit 1.)

2 Excerpt of May 2011 LEXAPRO label. (Schaefer Dec., Exhibit 2.)

3 Dr. Healy is the only witness plaintiffs have identified as an expert on general causation. Apart from Dr. Healy, plaintiffs identified one other expert, Michael Hamrell, Ph.D. Dr. Hamrell is proffered as plaintiffs' warnings expert. At his deposition, Michael Hamrell testified that he will not provide opinions regarding causation. (Schaefer Dec., Exhibit 3, pp. 51-52.)

In Dr. Healy's opinion, CELEXA and LEXAPRO cause suicide. He claims that they do so by causing akathisia (a movement disorder), emotional blunting, and psychotic decompensation in persons taking those medications. (Schaefer Dec., Exhibit 4, Healy Report, p. 1.) In forming his opinions, Dr. Healy relies on five purported categories of "evidence for General Causation": (1) the relationship between CELEXA and LEXAPRO; (2) "healthy volunteer studies" involving SSRI antidepressants; (3) his analysis of data from CELEXA and LEXAPRO clinical trials; (4) proposed mechanisms through which CELEXA and LEXAPRO may trigger suicide; and (5) alleged wholesale "ghostwriting" of scientific articles. (Schaefer Dec., Exhibit 4, p. 10.) Dr. Healy's opinion that this "evidence" demonstrates that CELEXA and LEXAPRO cause suicide is deeply flawed and should be excluded.

In 2002, in a case involving allegations that the antidepressant ZOLOFT®[4] caused suicide, a federal district court excluded the testimony of David Healy noting that "Dr. Healy's view as to general causation is a distinctly minority view." *Miller v. Pfizer*, 196 F.Supp. 2d 1062 (D. Kan. 2002), *affirmed*, 356 F.3d 1326 (10th Cir. 2004). (Schaefer Dec., Exhibit 6.) In *Miller*, as here, Dr. Healy placed heavy reliance on his own "healthy volunteer" study of 20 persons, published in 2000. *Miller* at 1067. In *Miller*, as here, Dr. Healy proposed that the medication caused akathisia and "emotional indifference" which, according to him, lead to suicide. *Id.* at 1066. Here, as in *Miller*, Dr. Healy relies upon calculations he makes from data published by others, and his calculations have not been subjected to peer review. "Regardless of the reason *why* Dr. Healy's numbers have not been subject to publication and peer review, the lack of peer review means that the Court simply does not have the assurance of reliability that this *Daubert* factor would normally provide." *Id.* at 1073.

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[4] ZOLOFT is a member of the same class of antidepressants as CELEXA and LEXAPRO. It is a selective serotonin reuptake inhibitor, or SSRI, marketed by Pfizer Inc.

In implicating CELEXA and LEXAPRO with suicide, Dr. Healy persists in using, virtually unchanged, the unscientific and unreliable methods he unsuccessfully attempted to rely upon in *Miller* ten years ago. His proposed testimony in *Miller*, proffered by some of the same counsel here, was thoroughly evaluated by the federal district court judge in Kansas. That judge appointed independent experts (apparently at plaintiffs' request) to review the methods employed by Dr. Healy. The judge conducted an evidentiary *Daubert* hearing at which Dr. Healy was questioned. After this inquiry, the judge found Dr. Healy's methods lacking and excluded his testimony, issuing a lengthy opinion discussing Dr. Healy's methods in great detail. Dr. Healy's exclusion was affirmed by the Tenth Circuit Court of Appeals in 2004. *Miller v. Pfizer*, 356 F.3d 1326 (10th Cir. 2004). (Schaefer Dec., Exhibit 7.)

Over many years, Dr. Healy has given lectures, operated one or more Internet websites and written general interest books[5] critical of the growth in antidepressant use and promoting his belief that SSRI antidepressants (inclusive of CELEXA and LEXAPRO) cause suicide. Those opinions are his stock in trade. The *Miller* court correctly perceived that Dr. Healy's singular approach and his "distinctly minority view" misuse the evidence and reject the methodologies that medical science accepts as reliable and trustworthy. What was true in *Miller* is true here. For this reason, Dr. Healy's testimony should be excluded as failing to meet the requirements of Fed. R. Evid. 702.

There have been intervening occasions in which Dr. Healy has been permitted to testify. However, Dr. Healy's participation in those intervening cases does not refute the conclusions of the court in *Miller* or the evidence and arguments Forest presents here. What Dr. Healy offered as scientific evidence in *Miller* is offered again in this litigation even though his conclusions are not shared by FDA or consistent with the conclusions found in the scientific literature.

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[5] E.g., David Healy, LET THEM EAT PROZAC (2004); David Healy, THE ANTIDEPRESSANT ERA (1997); and most recently, David Healy, PHARMAGEDDON (2012).

Here, Dr. Healy's lengthy report and deposition testimony reveal that his methods as applied to CELEXA and LEXAPRO are no better than (and in some respects, are much worse than) the methods that were properly rejected by the *Miller* court more than ten years ago. Here, Dr. Healy was confronted at deposition with significant issues he admitted he never considered. His responses, admissions and attempted justifications "on the fly," when confronted with new data that conflict with the limited and cherry-picked data he chose to rely upon, highlight the shortcomings in his methods. New and contrary information is not a threat to fair-minded scientific inquiry. However, it is a threat to close-mindedness and to book sales.

III. STATEMENT OF FACTS

CELEXA and LEXAPRO are prescription medications approved by FDA to treat major depressive disorder. In the United States, CELEXA was approved in 1998; LEXAPRO was approved in 2002. In 2003, LEXAPRO was approved to treat generalized anxiety disorder and, most recently, in 2009, was approved to treat adolescent depression. Both CELEXA and LEXAPRO are among the class of antidepressants known as "SSRIs," described more fully below.

CELEXA and LEXAPRO contain active ingredients that are chemically related. LEXAPRO contains substantially pure escitalopram ("S-citalopram"). CELEXA contains an equal measure of escitalopram and its mirror image isomer commonly known as "R-citalopram." The R-citalopram in CELEXA does not provide a therapeutic benefit and is believed to inhibit the activity of escitalopram. Mixtures of mirror image isomers, such as citalopram, are termed "racemic mixtures." They are not unusual in synthetic biochemical products. For example, compounds such as synthetic Vitamin E (dl-alpha tocopherol acetate) are racemic mixtures of optical isomers.

The term "SSRI" is used to describe a chemically diverse class of medications that include CELEXA and LEXAPRO. SSRI means "Selective Serotonin Reuptake Inhibitor." This refers to an effect of SSRI medications that affects the bioavailability of the neurotransmitter serotonin in nerve cells. Serotonin is one of a number of neurotransmitters that can be released by a neuron to "signal" an adjacent nerve cell. Once the serotonin has delivered a signal to a target cell by becoming bound to a serotonin receptor on the surface of the target cell, it is released by the cell and can be reabsorbed by another cell in a form of neural "recycling." SSRIs as a class inhibit the "re-uptake" of unbound serotonin by nerve cells.

The individual SSRI compounds, however, are chemically distinct in structure and have different pharmacokinetic and pharmacologic properties. Notably, there is no functional molecular structure identified in SSRI antidepressants that is a common "key" to their serotonin reuptake inhibition properties.

The inhibition of serotonin reuptake by SSRI medications is observable soon after they are ingested, but it is known and accepted that achieving the antidepressant effect of SSRIs may require days or weeks of using the drugs as directed. In addition, depression is a complex psychiatric condition, and research has shown that not all depressed persons are helped by SSRI antidepressants.

In addition to SSRI antidepressants, other antidepressant medications exist. Some affect the reuptake of other neurotransmitters, such as venlafaxine (EFFEXOR®), which affects reuptake of both serotonin and the neurotransmitter norepinephrine (thus termed an "SNRI"). There are two other classes of antidepressants, in use prior to the availability of SSRI antidepressants. They are monoamine oxidase inhibitors (MAOI) and tricyclic antidepressants (TCA). Those medications affect serotonin chemistry in different ways and are not selective serotonin reuptake inhibitors. MAOI and TCA antidepressants are generally less prescribed

today, in part due to their greater risks of toxic adverse events, including overdose, in comparison to SSRI compounds.

Plaintiffs here allege that both CELEXA and LEXAPRO cause persons to commit suicide when taken as prescribed. They claim that the warnings/labeling of CELEXA and LEXAPRO were inadequate to properly warn of the risks of suicide allegedly caused by the medications. But the science simply does not support the conclusion that CELEXA or LEXAPRO causes suicide.

The FDA never has required labeling of antidepressants to state that CELEXA, LEXAPRO, or any SSRI causes suicide in any population of patients. In fact, the current boxed warning demonstrates FDA has found just the opposite with respect to all but one of the decedents at issue in this MDL:[6]

> Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-terms studies of major depressive disorder and other psychiatric disorders. Anyone considering the use of [CELEXA/LEXAPRO] or any other antidepressant in a child adolescent or young adult must balance this risk with the clinical need. **Short-terms studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older.** Depressions and certain psychiatric disorders are themselves associated with increases in the risk of suicide.[7]

Antidepressant medications are used to treat depression, and depression is among the most significant risk factors for suicidal thoughts and acts, including suicide itself. In addition, depression is linked to comorbidities such as anxiety and substance abuse. Those comorbidities

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6 All but one decedent in this MDL was 25-years of age or older when they were prescribed CELEXA or LEXAPRO (and when they committed suicide). Two were 65-years-old or older when they were prescribed LEXAPRO.

7 Schaefer Dec., Exhibit 2 (emphasis added).

are themselves significant risk factors for suicide.[8] There has been extensive inquiry, by medical science and by FDA, into whether there is reliable evidence of a causal relationship between antidepressant use and completed suicide. No such link has been shown for antidepressants in general, or for CELEXA and LEXAPRO in particular.

Since Dr. Healy's methods were first rejected in *Miller*, FDA has, on several occasions, convened advisory committees to consider publicly whether there is a relationship between antidepressants and the emergence of suicidal thoughts and acts. In 2004, an advisory committee recommended a "black box" warning of the emergence of suicidality (i.e., suicidal thoughts and acts) in depressed adolescents using antidepressants. This recommendation came after FDA review and meta-analysis of drug company spontaneous adverse event report data from numerous adolescent clinical trials. In those trials, increased incidence of suicidal thoughts and acts were observed more frequently in children and adolescents taking study medications as compared to placebo. There were no completed suicides in any of the studies.[9]

In 2006, a second advisory committee was convened to consider another extensive FDA meta-analysis. Meta-analysis is a method for pooling results of multiple studies.[10] This advisory committee considered FDA's meta-analysis of adverse event reporting data involving more than 100,000 adult clinical trial participants. FDA found no statistically significant association between antidepressants (including CELEXA and LEXAPRO) and suicidal thoughts and acts for

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8 American Society for Suicide Prevention, Risk Factors for Suicide, available at http://www.afsp.org/index.cfm?page_id=05147440-E24E-E376-BDF4BF8BA6444E76 (Schaefer Dec., Exhibit 8.)

9 Tarek A. Hammad, et al., "Suicidality in Pediatric Patients Treated With Antidepressant Drugs," Arch Gen Psychiatry 2006; 63: 332-339. (Schaefer Dec., Exhibit 9.)

10 Michael D. Green, et al., *Reference Guide on Epidemiology*, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 3d 606-607 (2011) ("Reference Manual").

adults above age 24.[11] In this large group of study participants, there were so few completed suicides (eight) that no valid scientific evidence could be obtained regarding suicide.[12]

Ultimately, FDA did require a warning about antidepressant use and suicidal acts, but only for persons up to age 24. FDA also required that the package insert state there was no observed relationship between suicidality and antidepressant after age 24, and that there was a protective effect after age 65.[13] Subsequent research has not confirmed FDA's hypothesis of no effect upon suicidality from ages 25-64, but has found evidence of a strongly protective effect from suicidal acts for all adults.[14] A more detailed discussion of the regulatory history of antidepressants and the question of suicide is presented in Forest's Motion to Exclude the Testimony of Michael Hamrell, Ph.D., and that discussion is incorporated by reference herein.

IV. APPLICABLE LAW

Under Fed. R. Evid.. 702, , the courts are charged as gatekeepers to screen expert testimony for its reliability. *Lauzon v. Senco Products, Inc.*, 270 F.3d 681, 686 (8th Cir. 2001) (*citing Daubert v. Merrell Dow Pharm.,* 509 U.S. 579, 591-93 (1993)). And, the proponent of expert testimony bears the burden to prove its admissibility by a preponderance of the evidence. *Id.* at 685-86.

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11 Mark Stone, et al., "Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration," BMJ 2009; 339: b2880. (Schaefer Dec., Exhibit 1.)

12 Id. at p. 4; *See also* FDA Presentation by Marc Stone, MD, at December 13, 2006, meeting of the Food and Drug Administration Center for Drug Evaluation Research, Psychopharmacologic Drugs Advisory Committee. (Schaefer Dec., Exhibit 10, p. 58.)

13 Excerpt of May 2011 LEXAPRO® label. (Schaefer Dec., Exhibit 2.)

14 Corrado Barbui, et al., "Selective serotonin reuptake inhibitors and risk of suicide: a systematic review of observational studies," CMAJ 2009; 180(3): 291-7. (Schaefer Dec., Exhibit 11.); Andrew C. Leon, et al., "Antidepressants and Risks of Suicide and Suicide Attempts: A 27-Year Observational Study," J Clin Psychiatry 2011; 72(5): 580-586. (Schaefer Dec., Exhibit 12.); Robert D. Gibbons, et al., "Strategies for Quantifying the Relationship between Medications and Suicidal Behaviour, What has been Learned?" Drug Saf 2011; 34(5): 375-395. (Schaefer Dec., Exhibit 13.)

Fed. R. Evid. 702 has three subparts that are prerequisites for the admission of proposed expert testimony. First, the testimony must be useful in deciding the ultimate issue of fact. Second, the proposed expert must be qualified. Third, the testimony must be reliable or trustworthy. *Lauzon* at 686. In assessing the reliability of the proposed testimony, Rule 702 codifies the principles established in *Daubert* requiring that (1) the testimony is based upon sufficient facts or data; (2) the testimony is the product of reliable principles and methods; and (3) the principles and methods have been applied reliably to the facts of the case. *Id., quoting* Fed. R. Evid. 702 and Comm. Note thereto.

To establish that an expert's methodology is reliable requires "a showing that the methodology is generally applied properly to the facts at issue in the case based on *scientifically accepted methodology*." Evidence must be validated by more than the *ipse dixit* statement by a purported expert that "I say it's valid, therefore it must be valid." *Arnold v. Amada North America, Inc.*, 77 Fed. R. Evid Serv. 248, 2008 WL 2411789 *2 (E.D. Mo. 2008) (citing *Daubert* at 589-90; *General Electric v. Joiner*, 522 U.S. 136, 146 (1997) (emphasis in original). *Daubert* established four non-exclusive factors courts could consider in evaluating the reliability of an expert's methods: (1) whether a theory or technique has been, or can be, tested; (2) whether a theory or technique has been subject to peer review and publication; (3) whether a theory or technique has a known or potential rate of error; (4) whether a theory or technique has become generally accepted. *Daubert* at 593-594.

The Eighth Circuit has recognized that additional factors can aid a proper analysis of admissibility, including whether the testimony was developed for litigation, whether the proposed expert ruled out alternative explanations, and whether the expert sufficiently connected the testimony to the facts of the case. *Lauzon* at 688.

Here, Dr. Healy's *qualifications* are not being challenged by Forest to the extent his testimony is limited to the question of general causation as disclosed in his report and at deposition. Should Dr. Healy attempt to offer expert testimony on other topics, Forest reserves the right to object to such testimony on all legal grounds, including lack of qualifications.

As shown below and as explained in the reports of Forest's experts, Dr. Healy's testimony is not based upon sufficient facts and data and is not the product of reliable principles and methods. Much of what Dr. Healy relies upon is irrelevant. He ignores data that casts doubt upon the validity of his methods and conclusions. His methods and views are not generally accepted. His methods of using data from others and performing his own calculations on that data to support his opinions have not been subject to peer review. His testimony is based in part upon irrelevant accusations about the drug industry as a whole, but he has made no investigation as to any conduct by Forest. It should be excluded.

V. DR. HEALY'S METHODS, CONCLUSIONS AND OPINIONS REGARDING CELEXA AND LEXAPRO ARE FATALLY FLAWED

In the Healy Report, Dr. Healy lists the following as his opinions in this case regarding CELEXA and LEXAPRO:

- "LEXAPRO & CELEXA can make individuals who may not have been likely to commit suicide before taking the pill, more likely to do so while on treatment."
- "LEXAPRO & CELEXA can cause some people to experience akathisia, emotional dysregulation, and psychotic decompensation, which can result in acts of self-harm, including suicide."
- "Clear warnings regarding suicide on this drug would [sic] have been appropriately placed on it from the date of its launch and [ ] such warnings would have saved lives."[15]

(Schaefer Dec., Exhibit 4, Healy Report, p. 1.)

15 At deposition, plaintiffs' counsel stated that Dr. Healy was not being offered by plaintiffs as a labeling expert. (Schaefer Dec., Exhibit 5, pp. 41-42.)

Dr. Healy "methodology" has five major components, or as he refers to them, "Evidence for General Causation":

- "First, I will look at the relationship between CELEXA (citalopram) and LEXAPRO (escitalopram)."
- "Second, I will look at healthy volunteer studies done with SSRIs."
- "Third, I will consider the data from CELEXA and LEXAPRO clinical trials."
- "Fourth, I will review the mechanisms through which LEXAPRO/CELEXA may trigger suicide."
- "[F]inally, I will look at the issue of ghost writing of scientific articles . . ."

(Schaefer Dec., Exhibit 4, Healy Report, p. 10.)

As a framework to analyze the flaws in Dr. Healy's methodology, those five components, as he proposes to apply them to Forest, CELEXA, and LEXAPRO in support of his opinions, will be discussed in turn below. Critically, Dr. Healy's failure to address a large body of epidemiological data that contradicts his opinions is fatal to the admissibility of his testimony.

A. Dr. Healy's discussion of the relationship between CELEXA and LEXAPRO is wholly irrelevant to a reliable scientific inquiry into whether either of those medications causes suicide -- It is merely background information

Beginning on page 10 of the Healy Report, and comprising seven single spaced pages under the heading "1/Origins of LEXAPRO/CELEXA," Dr. Healy provides a rambling editorial narrative that presents his views on the development of antidepressants. After four pages of what can only be described as background material, Dr. Healy finally gets around to a discussion of escitalopram and citalopram. In the three pages that follow, Dr. Healy goes on at length about the issue whether escitalopram and citalopram are effective medications. In particular he focuses

upon critiquing the evidence that escitalopram is more effective than citalopram.[16] There is no mention in those pages of suicide or even suicidality as an adverse event associated with antidepressant use – either in general or as to CELEXA and LEXAPRO in particular. Dr. Healy offers no explanation why this topic is of any significance to his opinions that CELEXA and LEXAPRO both cause suicide.

Appendix 1 to his report, beginning at page 40, contains an additional four pages of single-spaced commentary that begins "Forest claim [sic] that LEXAPRO has superior efficacy, tolerability, and earlier time of onset of action compared to CELEXA and other drugs." In this Appendix, which does not appear to be referenced in the main body of Dr. Healy's report, Dr. Healy again embarks upon a critical essay on the question of whether escitalopram is more effective than citalopram. Like pages 10-16 earlier in the report, these Appendix pages contain no mention of the topics of suicide or suicidality.

Reviewing these pages, one would be justified in wondering what litigation they pertain to. This material is never "connected up" by Dr. Healy. He never explains how his views on antidepressant development and about the efficacy of escitalopram in comparison to citalopram are relevant to whether CELEXA and LEXAPRO cause suicide. Apart from the lack of evidentiary relevance, the Eighth Circuit has stated that such a gap or lack of "fit" is a consideration in a *Daubert* analysis of an expert's methodologies. *Lauzon* at 688.

Ultimately, struggling through these pages looking for anything relevant to explain why Dr. Healy has included this material as one of his five categories of "evidence for General Causation" is unavailing. The material within these pages of Dr. Healy's report has no perceivable relevance to the opinions Dr. Healy purports to offer. It is, however, relevant to this

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[16] Dr. Healy testified that he prescribes citalopram, but not escitalopram, in his clinical practice. (Schaefer Dec., Exhibit 5, p. 340.)

Daubert motion because it shows that Dr. Healy's methods, as revealed by his use of irrelevant materials as "evidence for General Causation," are unreliable.

B. Dr. Healy's persistent reliance upon his own "healthy volunteer study" by the *Miller* court

Dr. Healy states that as "evidence for General Causation," he relies upon "healthy volunteer studies done with SSRIs." Dr. Healy claims that these studies show that antidepressants trigger suicide in persons taking them who are "healthy volunteers" and are not depressed.[17] According to Dr. Healy, however, none of those studies involved CELEXA or LEXAPRO.

Dr. Healy believes that data from healthy volunteer studies are "extremely important" and that "healthy volunteer trials are among the clearest tests of a drug."[18] Thus, the Court must closely scrutinize his methods and the materials he chooses to rely upon regarding healthy volunteer data if his testimony is to be allowed. As will be shown, scrutiny of his methods reveals that they are not reliable.

In the section of his report entitled "2/Healthy Volunteer Studies," Dr. Healy embarks upon another historical essay. He cites his own editorial[19] as evidence that in 1955, a plant-derived drug called RESERPINE, used to treat hypertension, caused suicides in "patients who had no nervous problems – i.e. essentially healthy volunteers."[20] Dr. Healy likens RESERPINE to SSRIs such as CELEXA and LEXAPRO claiming that "it also acts on the serotonin system.

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17 Schaefer Dec., Exhibit 5, pp. 17-21.

18 Schaefer Dec., Exhibit 5, p. 122-123.

19 David Healy, et al., "RESERPINE exhumed," Br J Psychiatry 1998;172: 376-378. (Schaefer Dec., Exhibit 14.)

20 As will be shown, Dr. Healy's willingness in his report to characterize persons he had no experience with as "essentially healthy volunteers" does not extend to a willingness to agree that thousands of persons prescribed antidepressants for "non-psychiatric indications" were likewise "essentially healthy volunteers" in FDA research.

In fact, RESERPINE is known to cause depression, and depletes serotonin, rather than preventing its reuptake (i.e., increasing its availability).[21]

Continuing, Dr. Healy states, "I have reviewed the healthy volunteer trials of paroxetine (PAXIL®) and sertraline (ZOLOFT) in detail." He then describes his methodology with respect to investigating healthy volunteer data for CELEXA and LEXAPRO: "I see no reason to believe the studies undertaken with citalopram or escitalopram differ to[sic] those done with PAXIL or ZOLOFT." (Schaefer Dec., Exhibit 4, Healy Report, p. 18.) This is imputation and not a scientific methodology at all.

The PAXIL and ZOLOFT studies Dr. Healy claims to be familiar with are not cited in his report or disclosed as part of plaintiffs' Rule 26 obligations. They were not produced at his deposition.

Dr. Healy's report does sketchily summarize some evidence he apparently has extracted from these undisclosed reports. (*See* Schaefer Dec., Exhibit 4, Healy Report, pp. 18-19.) There, Dr. Healy is critical of the conduct of the PAXIL and ZOLOFT studies and describes a number of adverse events that purportedly arose such as mood change, tremor, agitation, "turmoil" and sexual dysfunction. Those events, presuming that they occurred, are not suicide, and Dr. Healy does not disclose a rationale to support the relevance of those events to the question whether CELEXA and LEXAPRO cause suicide. As to suicide, Dr. Healy claims that in one PAXIL study, a volunteer "committed suicide following the study."

Dr. Healy also claims knowledge of a suicide during a healthy volunteer study by a person taking the SNRI antidepressant duloxetine (Cymbalta).[22] (Schaefer Dec., Exhibit 4,

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21 *See* Schaefer Dec., Exhibit 15, May 31, 2012, Expert Report of Stephen M. Stahl, M.D., Ph.D., pp. 46-47; *See also* Schaefer Dec., Exhibit 5, Healy Dep., pp. 260-262.

22 While he makes only passing reference to this death, Dr. Healy did disclose the name of the decedent, Traci Johnson. Dr. Healy does not disclose that at the time of her suicide in 2004, Ms. Johnson reportedly had been on placebo medication for four days after her medication dose was tapered to 0. Nor does he

Healy Report, pp. 18-19.) Dr. Healy discloses no other facts about those suicides, and does not describe whether he knows anything about them that supports a conclusion that they were related to the medications being studied.[23] Dr. Healy's methods of analysis are not disclosed and cannot be evaluated.

At his deposition, Dr. Healy was specifically asked about his knowledge of CELEXA and LEXAPRO healthy volunteer studies. All he could say was "I have not reviewed the healthy volunteer studies in detail . . . I mean I can confirm for you, for instance, that healthy volunteer studies were done."[24] (Schaefer Dec., Exhibit 5, Healy Dep., p. 119.) Dr. Healy, having never reviewed results of any citalopram and escitalopram healthy volunteer studies, merely assumed that all SSRIs produce the same outcomes when given to healthy volunteers. (Schaefer Dec., Exhibit 5, Healy Dep., p. 121.) His support for this assumption was that he had knowledge of others' opinions in the field who had reached this conclusion. (Id.) So, the entirety of Dr. Healy's "evidence for General Causation" regarding healthy volunteer data is devoid of any evidence regarding CELEXA and LEXAPRO.

The centerpiece of Dr. Healy's healthy volunteer evidence is his own study of 20 selected workers from the North Wales district general hospital psychiatric unit. In this study, volunteers who were "not currently depressed" were given either reboxetine (an SNRI not approved in the

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disclose that FDA actually investigated the death and determined that it could not be linked to the medication. *See, e.g.*, Walter F. Naedele, "FDA: Drug was not tied to death. Medication Traci Johnson took in a clinical study was not linked to her suicide, agency says." *Philadelphia Inquirer*, August 13, 2004, available at http://articles.philly.com/2004-08-13/news/25393466_1_duloxetine-cymbalta-suicide. (Schaefer Dec., Exhibit 16.)

23 In fact, Dr. Healy never states that he has concluded that those two suicides were caused by the medications, noting about the PAXIL case, "*It cannot be assumed that this suicide did not stem from PAXIL*." (Exhibit 4, Healy Report, p. 19.)

24 In the conclusion to his report, Dr. Healy states: "There is a compelling case that LEXAPRO® & CELEXA® can induce suicidality in subjects who take it whether they are being given this drug for depression or post-menopausal flushing or for other conditions." (Schaefer Dec., Exhibit 4, Healy Report, p. 38.) Having testified that he never looked at healthy volunteer study data involving CELEXA® or LEXAPRO®, it is unclear where he came up with "post-menopausal flushing" and what evidence about CELEXA® and LEXAPRO® he finds compelling in this regard.

United States) or sertraline (ZOLOFT) for two weeks. Then, following a two-week washout period with no medications, the other medication, i.e., the one not taken during the first two weeks, was given for a two-week period. According to Dr. Healy, during the study "two subjects taking sertraline developed clear suicidal ideation." This amounted to 10% of the 20 participants. This study was published, with Dr. Healy as sole author, in 2000.[25]

Not surprisingly, as it involved ZOLOFT, this study was a basis for Dr. Healy's opinions in *Miller v. Pfizer*. His misplaced reliance upon it there, as evaluated from a methodological perspective by court-appointed expert, Dr. John Concato, formed part of the rationale for excluding his testimony. (Schaefer Dec., Exhibit 6, *Miller* at 1074-76.) Dr. Concato's report *here* likewise explains that Dr. Healy's so-called "healthy volunteer" study is an example of "qualitative research" and that a methodology that relies upon this research as evidence of causation is flawed.[26] (Schaefer Dec., Exhibit 18, Report of John Concato, M.D., M.S., M.P.H. (hereinafter "Concato Report"), p. 9-16.)

The Healy study is flawed for at least three reasons and reliance upon it as evidence of causation is an unsound methodology. First, although the study purported to be a randomized trial, its results were not the product of the randomized design but were entirely subjective, gathered by focus group and resulting in publication of what are essentially two case reports and not clinical trial data. (Schaefer Dec., Exhibit 18, Concato Report, p. 10-11.) The published study results revealed a qualitative approach which "is largely inductive, allowing meaning to

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25 David Healy, "Emergence of antidepressant induced suicidality," Primary Care Psychiatry 2000; 6(1): 23-28. (Schaefer Dec., Exhibit 17.)

26 There also is published commentary critical of this study. *See* Patricia Casey, "SSRI and Suicide," Psychotherapy & Psychosomatics 2004; 10: 259-260. (Schaefer Dec., Exhibit 19.)

emerge from the data . . . ."[27] In the *Daubert* hearing in *Miller*, Dr. Healy admitted as much about his study. According to the judge:

> During the *Daubert* hearing, Dr. Healy admitted that his Healthy Volunteer Study was not designed to research treatment-emergent suicidality and that any conclusions regarding that phenomenon were a by-product of the study results – not the design.

Schaefer Dec., Exhibit 6, *Miller* at 1074.

Second, the Healy study was flawed because "the participants had multiple opportunities to be influenced by the beliefs held by the author[] . . ." and this influence, invariable in qualitative research, must be made explicit in published qualitative research. "It was not made explicit in the 'Healy study'" (Schaefer Dec., Exhibit 18, Concato Report, p. 12.) Dr. Healy agreed:

> Dr. Healy also agreed with the independent experts that subliminal communication between the researchers and the volunteers may have influenced the results. In particular, before the study, Dr. Healy gave the subjects detailed information regarding the side effects of each drug.

Schaefer Dec., Exhibit 6, *Miller* at 1074-75.

Third, reliance upon the Healy study of 20 persons is flawed because its reported frequency of 10% of the participants becoming suicidal while taking antidepressants is not consistent with, and differs greatly from, recently published FDA data gathered from multiple sources and involving thousands of "essentially healthy volunteers." Dr. Healy's continued reliance upon his study is therefore an unsound methodology.

As explained more fully at pages 13-16 in Dr. Concato's report, and as discussed during Dr. Healy's deposition at pages 245 through 258, FDA's 2005 meta-analysis of adult suicidality data from clinical trials of antidepressants included data on over 13,000 persons who were

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[27] *Id.*, quoting Ayelet Kuper, et al., "An introduction to reading and appraising qualitative research, BMJ 2008; 337: 404-405. (Schaefer Dec., Exhibit 20.)

prescribed antidepressants for non-psychiatric indications. FDA listed those indications, which included smoking cessation, obesity, fibromyalgia, stress urinary incontinence, etc.[28] As explained by Dr. Marc Stone, one author of the FDA research, there were so few adverse events characterizable as possibly related to suicide among those study participants that the entire dataset was excluded from further consideration in his Clinical Review.[29]

In particular, there were only 12 suicide-related adverse events among the more than 13,000 persons taking antidepressants (i.e., not placebo) for non-psychiatric reasons. Eleven of those adverse events involved ideation only (thoughts of suicide). There was one suicide attempt. (*See* Schaefer Dec., Exhibit 18, Concato Report, p. 14; *see also* Schaefer Dec., Exhibit 21, Levenson Paper, p. 27.) Those 12 events amounted to just under 0.1% of the persons taking antidepressants for non-psychiatric reasons in comparison to the 10% Dr. Healy testified that his study of 20 healthy volunteers detected. (Schaefer Dec., Exhibit 5, Healy Dep., pp. 257-258.)

Dr. Healy never considered this information published by FDA before being deposed. (Schaefer Dec., Exhibit 5, Healy Dep., pp. 250-251.) Nevertheless, he immediately refused to agree that persons taking antidepressants for non-psychiatric indications could be considered healthy volunteers, despite being willing to consider as "essentially healthy volunteers" persons he read about who took RESERPINE for hypertension in 1955. (Schaefer Dec., Exhibit 4, Healy Report, p. 17; s*ee* p. 15, *supra* and n. 21.) While Dr. Healy came up with a number of excuses why he would not agree to consider the study participants as healthy volunteers, none was based

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[28] Mark Levenson, et al., "Statistical Evaluation of Suicidality in Adults Treated with Antidepressants," November 17, 2006 (Briefing Materials for December 13, 2006, meeting of Food and Drug Administration Center for Drug Evaluation and Research Psychopharmacologic Drug Advisory Committee.), pp. 52-53 ("Levenson Paper"). (Schaefer Dec., Exhibit 21.)

[29] Marc Stone, et al., "Clinical Review: Relationship Between Antidepressant Drugs and Suicidality in Adults," November 17, 2006 (Briefing Materials for December 13, 2006, meeting of Food and Drug Administration Center for Drug Evaluation and Research Psychopharmacologic Drug Advisory Committee), p. 22 ("Clinical Review"). (Schaefer Dec., Exhibit 22.; s*ee also* Schaefer Dec., Exhibit 1, Stone Paper, p. 4.)

upon any facts about the participants in the study data submitted to FDA. In fact, Dr. Healy testified that he did not consider examining the studies submitted to FDA to be worthwhile.[30]

Dr. Healy's on-the-fly attempts to try to preserve the importance of his own small study were pure speculation. As the REFERENCE MANUAL ON SCIENTIFIC EVIDENCE acknowledges, "[t]he scientific enterprise must always remain open to reassessing the validity of past judgments as new evidence develops."[31] Rather than embrace this ideal, Dr. Healy resorted to his playbook and made speculative rationalizations why this recent FDA data was not significant healthy volunteer data that called into question his own research and conclusions. (Schaefer Dec., Exhibit 5, Healy Dep., pp. 246-256.)

Finally though, Dr. Healy partly capitulated:

Q In any event, can we agree that the incidence rate is more than 100 times less than what you found in your healthy volunteer study?

Dr. Healy We can.

Q Okay, and as we sit here today, understanding you haven't considered the question before, do you have any explanation for those results?

Dr. Healy No, I don't have any explanation.

(Schaefer Dec., Exhibit 5, Healy Dep., p. 258.)

This all shows that today, even better reasons exist to reject Dr. Healy's reliance upon this healthy volunteer study than existed when the *Miller* court excluded his testimony in 2002.

C. Dr. Healy's methods of selecting and interpreting data from clinical trials are unscientific and unsupportable

On page 22 of Dr. Healy's report, his section of "evidence for General Causation" entitled "3/ Clinical Studies & Randomized Trials" begins. After some background discussion,

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30 "I didn't think it was worthwhile to do so. . . . It was not going to shed further light on an issue that I believe the depression trials settled fairly conclusively." (Schaefer Dec., Exhibit 5, Healy Dep., p. 245-246.)

31 Michael D. Green, et al., Reference Guide on Epidemiology, in REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 3d (2011), p. 598.

Dr. Healy introduces Table 1 on page 24 of his report stating that it contains "the initial data submitted to FDA on suicides and suicidal acts . . . ." (Schaefer Dec., Exhibit 4, Healy Report, p. 23.) Table 1 lists data for citalopram involving 4,168 patients who received the drug and 691 placebo patients. Table 1 states that for the patients taking citalopram, 2.38% committed suicide or a suicidal act whereas for patients on placebo, 1.59%, committed suicide or a suicidal act. The data Dr. Healy presented in Table 1 regarding citalopram will be discussed in detail below. Regarding all of the "Investigational Drug" data in Table 1, Dr. Healy calculated a number of odds ratios comparing suicidal acts and suicides by patients using the drugs to suicides and suicidal acts of patients on placebo. Those also will be discussed in detail below.

At the outset, Dr. Healy makes a major misrepresentation about Forest. In his report following Table 1, he states, "This data were obscured by company efforts to hide the risks by coding as placebo suicides and suicidal acts, events that happened during the washout and withdrawal phases of trials – as illustrated in Figures 1 and 2 below." (Schaefer Dec., Exhibit 4, Healy report, p. 24.) The figures Dr. Healy refers to, shown on page 26 of his report, are figures he has used over the years in various presentations including presentations to an FDA Advisory Committee.[32] Dr. Healy purports to show in his Figures 1 and 2 that suicidal acts during the screening phase of adult trials and during follow up (when the patients were not taking medication) were wrongly added to the data for placebo. Note that Figures 1 and 2 allege that those events occurred during "fluoxetine-paroxetine-sertraline adult trials." *They do not involve Forest, CELEXA, or LEXAPRO.*

Yet on page 24 Dr. Healy claims "this data were obscured by company efforts . . ." (including to the odds ratios he calculated in Table 1, which includes citalopram data). He never

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[32] PowerPoint presentation by David Healy to FDA Psychopharmacologic Drug Advisory Committee. Available at http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4272s1-00-index.htm. (Schaefer Dec., Exhibit 23.)

discloses that his so-called evidence of data being "obscured" has nothing to do with Forest, CELEXA, or LEXAPRO. This statement by Dr. Healy and his use of Figures 1 and 2 in his report only show that Dr. Healy's methods are biased, misleading, and unreliable. Asked about this statement at deposition and whether he had any evidence that Forest ever did anything inappropriate, Dr. Healy responded, "I haven't looked for it. It hasn't seemed necessary to look for it." (Schaefer Dec., Exhibit 5, Healy Dep., p. 93.)

1. The Odds Ratios Calculated by Dr. Healy Allegedly Based Upon Data in Table 1 are Unreliable, Cannot be Tested, and are the Result of Deliberate Manipulation

On pages 23 and 24 of his report Dr. Healy includes various odds ratios regarding antidepressants, suicide, and suicidal acts. Dr. Healy was asked how those figures were derived and how they related to *differing numbers* and confidence intervals he previously has published using this *same data*. When asked about figures published in an article Dr. Healy co-authored in 2005[33] that relied upon the same data but which reported different odds ratios, and significantly different confidence intervals, Dr. Healy explained that he had used various statistical software packages to calculate figures over time, but did not recall any particulars about how the odds ratio figures he reported on pages 23 and 24 of his report were derived. (*See* Schaefer Dec., Exhibit 5, Healy Dep., pp. 153-162.) Dr. Healy admits that the odds ratio figures in his Rule 26 report here have not been published in a peer-reviewed journal. (Schaefer Dec., Exhibit 5, Healy Dep., p. 162.) He also claims he never has used the data in Table 1 to calculate an odds ratio for CELEXA alone. (Schaefer Dec., Exhibit 5, Healy Dep., p. 164.)

Dr. Healy's methods in deriving his odds ratios cannot be said to be based upon a reliable scientific methodology. His methods cannot be replicated, or tested for reliability; nor can they be evaluated for error. Dr. Healy's calculations purporting to show odds ratios for suicide and

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[33] David Healy, et al., "Antidepressant drug use & the risk of suicide," International Review of Psychiatry June 2005; 17(3): 163-172. (Schaefer Dec., Exhibit 24.)

suicidal acts are not supported by a methodology that meets the standards stated in *Lauzon* or required by Fed. R. Evid. 702.

2. The CELEXA Data Dr. Healy Reports in Table 1 Was Cherry-Picked in an Effort to Create a False Impression of Association

In his report, Dr. Healy did not disclose where the data reported for CELEXA in Table 1 originated. At his deposition, however, Dr. Healy conceded that his Table 1 data was taken from an article in 2001 by Kahn, et al.[34] Dr. Kahn used data obtained from FDA to research whether it was medically ethical to conduct placebo-controlled trials with antidepressants. The issue was whether there was data showing that antidepressants prevented suicides and suicidal acts in comparison to persons taking placebo. In other words, if the data available to Dr. Kahn in 2001 provided persuasive support that antidepressants prevented suicide and suicidal acts in depressed persons, then giving placebo to depressed persons during future clinical trials of antidepressants would present ethical concerns.

The results of the data examined by Dr. Kahn and published in his paper in 2001 (including data for CELEXA) found no statistically significant difference in the occurrence of suicide or suicide attempts among persons using antidepressants in clinical trials versus persons given placebo.[35] At deposition, it was revealed that Dr. Healy cherry-picked a subset of data from Dr. Kahn's research and claims that this shows that the rate of suicide and suicidal acts in persons using CELEXA versus placebo as approximately 2.38%/1.59%, or 1.5. (*See* Schaefer Dec., Exhibit 4, Healy Report, p. 24.) These percentages, as reported by Dr. Healy in Table 1 pertaining to citalopram studies, are not found in the 2001 article by Dr. Kahn. Dr. Khan never

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34 Arif Khan, et al., "Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: a replication analysis of the Food and Drug Administration Database," International Journal of Neuropsychopharmacology 2001; 4: 113-118. (Schaefer Dec., Exhibit 25.)

35 *Id.*

reached this conclusion. The raw data shown by Dr. Healy in Table 1 is, however, present in the Kahn article, as discussed below.

Table 1 on page 24 of Dr. Healy's report lists 4,168 patients using CELEXA with 8 suicides and 91 suicide attempts. He reports 691 patients on placebo with 1 suicide and 10 suicide attempts. These numbers can be found in Dr. Kahn's 2001 paper, however, the analysis of this data by Dr. Healy, as more fully explained at pages 16 through 19 of the report of Dr. John Concato, is not used by Dr. Kahn and comprises a methodologically unsound manipulation of Dr. Kahn's data to reach a contrary conclusion.

As to the 4,168 patients taking citalopram and the 691 patients taking placebo, Dr. Kahn had data allowing him to calculate "patient exposure years." Considering the number of suicides and suicidal acts for this group based upon how long they were exposed to drug or placebo, *Dr. Kahn's results showed no increase* in suicide or suicidal acts in the group using citalopram compared to placebo. (Schaefer Dec., Exhibit 18, Concato Report, p. 18.) Dr. Healy's report concludes that these data show an elevated risk for persons using citalopram whereas Dr. Kahn's data and method of analysis do not. (Schaefer Dec., Exhibit 18, Concato Report, pp. 18-19.)

At deposition, Dr. Healy was questioned at length regarding his manipulation of the data he obtained from Dr. Kahn's 2001 article. First, Dr. Healy was questioned regarding his decision to use the results for the subset of 4,168 patients for which Dr. Kahn had exposure year data as opposed to the larger group of almost 20,000 patients reported by Dr. Kahn as the total citalopram data set. Dr. Healy's testified he ignored the much larger set of citalopram data because he speculated the smaller data set was more reliable, and had he used the larger data set, there would have been more information for citalopram than "all other antidepressants put together." (Schaefer Dec., Exhibit 5, Healy Dep., p. 147.) Thus, Dr. Healy discarded approximately 75% of the data available in 2001 from Dr. Kahn's article regarding the incidence

of suicide and suicidal acts in persons taking citalopram versus placebo. He did so to balance his Table 1 as to the other drugs while never disclosing that the data for citalopram as analyzed and published by the researchers who obtained it showed no increased risk of suicide or suicidal acts in comparison to placebo.

Defending his decision to use the smaller citalopram data subset from Dr. Kahn's article, but reject Dr. Kahn's analysis of that data by length of exposure, Dr. Healy stated, "I didn't use patient exposure year data. As I've indicated to you, I think it's the wrong approach to take." (Schaefer Dec., Exhibit 5, Healy Dep., p. 144.) In fact, Dr. Healy's manipulation of data to derive the numbers reported for citalopram in Table 1 is a flawed manipulation of data that reaches results not reported by the authors from whom the data is taken. Dr. Healy never discloses that his results are at odds with those of the source of his data. Dr. Healy rejects methodology that provides a fair basis for a comparison in favor of one that creates a "false impression of an association." (Schaefer Dec., Exhibit 18, Concato Report, p. 16-19.)

3. Dr. Healy Misuses Clinical Trial Data Regarding Suicide and Suicidality Both Generally, and as Pertains to FDA Analyses

Dr. Healy discusses FDA's Advisory Committee meeting held December 13, 2006, on pages 32 and 33 of his report. On page 33, Dr. Healy claims, "there was an increase in risk in the age bracket 18-64, as well as 25-64. In the case of 45-54 year olds, the data showed a 2.29 fold increase in risk, while the 45-64 year olds showed a 1.75 fold increase." As support for this statement, Dr. Healy cites Tables 16 and 18 from FDA's 2006 Clinical Review research paper provided to members of the FDA 2006 Advisory Committee and made publicly available. (Schaefer Dec., Exhibit 22, Clinical Review, pp. 26, 30.)

The figures Dr. Healy quotes are selected from individual age ranges reported in Table 18. However, Dr. Healy does not disclose that those individual point estimates were not statistically significant. Nor does Dr. Healy disclose that FDA in its analysis of this same data,

found no association with suicidality among adults older than 25, a modest protective effect in persons 25-64 and a stronger protective effect in persons 65 and older. (Schaefer Dec., Exhibit 22, Clinical Review, pp. 27, 29.)

This selective use of data, and the failure to acknowledge that his interpretation is at odds with the authors of the research providing the data, exemplifies the unscientific methodologies used by Dr. Healy. By failing to even acknowledge, much less explain or justify, that the original researchers reached the opposite conclusion when examining the same data, Dr. Healy fails to rule out alternative explanations as is required of acceptable methodology. *See Lauzon* at 688. This is not the only instance in which Dr. Healy takes FDA researchers' data, but ignores the researchers' analyses of their data.

Dr. Healy recites odds ratios taken from the FDA clinical review provided to Advisory Committee members in December 2006 in his report at page 29. (*See,* Schaefer Dec., Exhibit 22, Clinical Review, Table 16, p. 26.) Dr. Healy claims, "the figures for escitalopram show a greater risk than do the figures for any other antidepressant and the figures for citalopram are greater than for all antidepressants other than paroxetine." (Schaefer Dec., Exhibit 4, Healy Report, p. 29.) At deposition (remembering the chemical relationship between CELEXA and LEXAPRO (*See* p. 7, *supra*)), Dr. Healy was asked to explain his conclusions that escitalopram showed a "greater risk" than all other antidepressants, including citalopram. (Schaefer Dec., Exhibit 5, Healy Dep., p. 203.) Dr. Healy was unwilling to agree that the very wide confidence interval for the escitalopram data,[36] which was not statistically significant suggested that the data were unstable. (Schaefer Dec., Exhibit 5, Healy Dep., p. 204.)

Dr. Healy's explanation was, "so you can't compare the figures on one drug with the figures on the other drug as though they reflect the true risk from each drug." (Schaefer Dec.,

[36] Odds ratio 5.67, confidence interval 0.94-34.2, as shown in Table 16 where he obtained the data.

Exhibit 5, Healy Dep., p. 205.) He states, "I don't believe the intrinsic risk from the two drugs differ, though. I believe it's an increased risk for both drugs." (Schaefer Dec., Exhibit 5, Healy Dep., p. 206.) He continues, "I haven't said that means that those drugs are riskier." (Schaefer Dec., Exhibit 5, Healy Dep., p. 206.) Asked, "You would agree then that escitalopram and citalopram are no more risky than any other SSRI. Fair?" Dr. Healy responded, "We – we do not have data to answer that question…I don't know." (Schaefer Dec., Exhibit 5, Healy Dep., pp. 209-210.)

Indeed, FDA in conducting the research and reporting this data made no conclusions that escitalopram or citalopram differed from any other antidepressant in respect to risk. Quite the opposite. FDA looked at the drugs involved in their research and determined that apart from a potential difference regarding sertraline that suggested further research, there was no basis to isolate any SSRIs due to drug specific differences in risk of suicide or suicidality. (Schaefer Dec., Exhibit 22, Clinical Review, p. 39.) Dr. Healy, presuming he reviewed the entire document before selecting the data he put in his report, would certainly have noted this. In Dr. Stone's presentation to the 2006 PDAC (which Dr. Healy attended and at which he gave a public comment) Dr. Stone stated that the differences between drugs "could be a chance finding." (Schaefer Dec., Exhibit 10, Transcript, p. 77.) Dr. Healy does not disclose it or explain why *his* approach, *segregating* data for escitalopram and citalopram, was proper in view of FDA's decision that it was not merited.

With other data, as it suits him, Dr. Healy ignores favorable results for CELEXA and LEXAPRO. Dr. Healy's report presents Table 2, which is purported to contain figures for suicide and suicidal acts in trials of a number of drugs, as "sent to the U.K. Regulator." (Schaefer Dec., Exhibit 4, Healy Report, p. 30.) This table lacks headings to explain what the figures pertain to. At his deposition Dr. Healy admitted he took Table 2 from an earlier article he

had published. (Schaefer Dec., Exhibit 5, Healy Dep., p. 223.) He then admitted that it contains an error regarding escitalopram but did not know the correct number that should be in the report. (*Id*.) Dr. Healy was able to identify the columns in Table 2 of his report and testified that, left to right, they represented "suicides on drug," "suicides on placebo," "suicidal acts on drug," and "suicidal acts on placebo." (Schaefer Dec., Exhibit 5, Healy Dep., pp. 224, 225.) Given this information, Dr. Healy admitted that looking at data for citalopram, it showed a protective effect as to suicide, saying, "it certainly doesn't look bad. That's correct." He agreed that, for escitalopram, the data in Table 2 show a relative risk of zero regarding suicide. (Schaefer Dec., Exhibit 5, Healy Dep., p. 225.)

In his report, Dr. Healy never discusses these individual favorable figures regarding citalopram and escitalopram. He only reports increased relative risks derived by his calculations of for all the drugs reported. Thus, his method as to Table 2 was to disregard the favorable individual results for citalopram and escitalopram while his method of using data from Table 16 of the FDA research paper was just the opposite. Dr. Healy's self-serving methods of manipulating data demonstrate that his opinions are unreliable. They certainly do not pass the threshold for expert testimony admissibility.

At deposition, Dr. Healy was asked:

> Q: Are you aware of anywhere in the worldwide literature of any report of a statistically significant incidence of suicide related to CELEXA or LEXAPRO?
>
> Dr. Healy: I don't know.

(Schaefer Dec., Exhibit 5, Healy Dep., p. 165.) Following up, Dr. Healy was asked more about FDA's Clinical Review of suicide and suicidality provided to the 2006 Advisory Committee tasked with reviewing the data. (Schaefer Dec., Exhibit 22, Clinical Review.) Dr. Healy, at page 30 in his report, had extracted data from this FDA document and cited Dr. Stone's paper on

pages 32 and 33. *It is part of what he relies upon.* At deposition, Dr. Healy was read the following excerpt of a presentation of the FDA research by Dr. Marc Stone, author of the Clinical Review paper:

> I thought at some point we ought to at least include the estimate for completed suicide, which you can see is higher than 1, but with very large confidence intervals who have only got 8 events among 100,000 subjects. That basically tells you that it is statistically meaningless. You really can't consider it to be any different than chance.

(Schaefer Dec., Exhibit 4, Healy Dep., p. 173.)

In response, Dr. Healy disagreed and claimed that FDA had indeed concluded that antidepressants cause suicide. He stated this repeatedly (Schaefer Dec., Exhibit 4, Healy Dep., pp. 167-169), but could offer no evidence to support the assertion. Dr. Healy alleged that he could locate a transcript in which FDA official, Dr. Russell Katz, stated "Antidepressants cause suicide." (Schaefer Dec., Exhibit 4, Healy Dep., p. 174.) When challenged to provide that "evidence," Dr. Healy subsequently provided a document containing FDA testimony excerpts showing only that some FDA officials, including Dr. Katz, had engaged in colloquy, over whether a statistically significant[37] association with *suicidality*, should one exist, was sufficient to establish causation of suicidality. (Schaefer Dec., Exhibit 26, Healy Supplement.) Astonishingly, some of the colloquy Dr. Healy cites took place during hearings over seizure medications, not antidepressants. (*Id.*) Dr. Healy's claim that FDA has officially concluded that antidepressants cause suicide is not supported by the evidence he proffered and is simply false.

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[37] Dr. Healy's proffer of statements by FDA officials, dealing with the threshold importance of a statistically significant association between a drug and suicidality-related clinical trial adverse events is at odds with statements in his deposition that applying statistical significance testing to reported adverse events is improper. "[A]s regards the non-primary outcome measures in clinical trials, I've testified repeatedly that it's not appropriate to – to pursue the issue of statistical significance." (Schaefer Dec., Exhibit 5, Healy Dep., p. 83; s*ee generally* also pages 84-89.)

The "evidence for general causation" presented by Dr. Healy under the heading "Clinical Studies & Randomized Trials" contains results that Dr. Healy has manufactured by improper manipulations of data published by other researchers. Dr. Healy has cherry picked data from other research without disclosing or justifying why his analysis of the data reached conclusions opposite of the researchers who published it. Dr. Healy has extracted data regarding CELEXA and LEXAPRO from others' research and compared it to data for other drugs to claim increased risks of CELEXA and LEXAPRO when the original researchers concluded there was no basis in their data to support treating drugs differently. At the same time, Dr. Healy does not separately consider data for citalopram and escitalopram from his own Table 2 where the results would have been more favorable in comparison to the risks he calculated and reported for all drugs combined.

Dr. Healy cannot identify any research that reports a statistically significant association between CELEXA, LEXAPRO, and suicide, but claims that FDA has concluded, "antidepressants cause suicide." The "support" he ultimately provides for this assertion not only does not contain the conclusion he alleges, but is essentially *obiter dicta* some of which involves antiseizure medications and not antidepressants. His methodologies regarding clinical study data fail to meet the requirement of Fed. R. Evid. 702 that testimony be the product of reliable principles and methods. He fails to meet this Court's requirement that admissible expert testimony be shown by the proponent to be "generally applied properly to the facts at issue in the case based on *scientifically accepted methodology*."[38]

D. Dr. Healy's "mechanisms" by which CELEXA or LEXAPRO "may trigger suicide" are not sufficiently reliable "evidence of General Causation."

The fourth component of Dr. Healy's "evidence of General Causation" begins on page 33 of his report and is entitled "4/ Mechanisms of Suicide Induction." It is just over three pages

[38] *Arnold v. Amada North America, Inc.*, 77 Fed. R. Evid Serv. 248, 2008 WL 2411789 (E.D. Mo. 2008).

long and has subsections entitled "A) Agitation/Akathisia," "B) Emotional Blunting," and Psychotic Decompensation." In Dr. Healy's opinion, those three conditions are adverse events caused by CELEXA and LEXAPRO and can lead to suicide. At deposition, Dr. Healy proposed additional "mechanisms of suicide induction" which will be mentioned below. None of those proposed mechanisms is reliable evidence that CELEXA and LEXAPRO cause suicide.

In beginning his discussion of "mechanisms of suicide induction," Dr. Healy states: "As outlined, there is solid evidence that there is an excess of suicidal acts found in clinical trials on SSRIs." (Schaefer Dec., Exhibit 4, Healy Report, p. 33.) In fact, as shown above, there is no such "solid evidence," only Dr. Healy's manufactured "evidence." Absent reliable and scientifically-accepted evidence of an association between CELEXA/LEXAPRO and suicide, the mechanisms Dr. Healy identifies cannot establish a causal relationship.

Where a reliable association between an exposure and an adverse event already has been established, the question whether there is a causal relationship responsible for the association is examined using a set of guidelines that date to 1965 and are sometimes referred to as the "Bradford-Hill criteria." These are:

1) Temporal relationship
2) Strength of the association
3) Dose-Response relationship
4) Replication of the findings
5) Biological plausibility
6) Consideration of alternative explanations
7) Cessation of exposure
8) Specificity of the association
9) Consistency with other knowledge.

REFERENCE MANUAL, p. 600. The Bradford-Hill criteria are guides for assessing possible causal relationships.[39]

In the absence of an established reliable association between CELEXA/LEXAPRO and suicide, relying upon the mechanisms below as Dr. Healy proposes as "evidence for General Causation" is an unacceptable methodology. As stated in the REFERENCE MANUAL, "In a number of cases, experts attempted to use [Bradford-Hill criteria] to support the existence of causation in the absence of any epidemiologic studies finding an association . . . but it does not reflect accepted epidemiologic methodology." (*Id.* at 599 n.141.)

In 2009, a federal district court in New Mexico excluded the testimony of Grace Jackson, M.D. (at the time an employee of one of plaintiff's counsel here) in *Rimbert v. Eli Lilly & Co*, No. 1:06-cv-00874 (D. New Mex. 2009). (Schaefer Dec., Exhibit 27.) The court in *Rimbert* held that it was a flawed "chain-of-events" methodology to use such purported mechanisms in support of general causation opinions. The *Rimbert* case involved a murder-suicide allegedly caused by Prozac. In rejecting the testimony of Dr. Grace Jackson, the *Rimbert* court makes specific reference to Dr. Healy's *Miller* causation opinions and their exclusion, quoting the *Miller* court as follows:

> Based on the testimony of its appointed independent experts, the [*Miller*] court found that [Dr. Healy's] methodology failed, concluding that:
>
> Generally accepted methodology in this case required [[Dr. Healy]] to consistently test the strength of association between SSRI drugs and suicide (the outcome of interest) – rather than the association between SSRI drugs and akathisia (which is purported to be part of the chain of events that lead to suicide, rather than an independent outcome.)

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39 While the *Miller* court referred to Dr. Healy's heavy dependence on such criteria (identified there as "Koch's Postulates," from which the very similar Bradford-Hill criteria were derived), here, Dr. Healy's report does not apply, cite or mention those or any other generally accepted alternative methods for assessing causal relationships. Thus, it is not possible to determine from his report what analytic method Dr. Healy relied upon to assess the "evidence for General Causation" in the five categories he disclosed.

Rimbert at 32, quoting *Miller v. Pfizer* at 1080. As in *Miller*, here Dr. Healy's proposed "mechanisms" are not reliable evidence to support the inference of a causal relationship between CELEXA/LEXAPRO and suicide. They are, at best, one alleged element in a complex analysis that has a condition precedent unmet on the facts here.

The "mechanisms" Dr. Healy proposes, as discussed below, may be examined as they pertain to the fifth Bradford-Hill criteria – biological plausibility, which considers whether there are plausible mechanisms to explain how an exposure can cause a result. As will be discussed below, even assuming *arguendo* that a reliable association has been established between antidepressants and suicide, the mechanisms Dr. Healy proposes are insufficiently reliable to serve as evidence of a causal relationship.

1. Agitation/Akathisia

On page 33 of his report, Dr. Healy claims that SSRIs cause agitation and akathisia. Akathisia is a movement disorder defined as "[a] condition of motor restlessness in which there is a feeling of muscular quivering, an urge to move about constantly, and an inability to sit still ...."[40] Dr. Healy claims that he has "written extensively on the emergence of the concept of akathisia." As support for this statement, he cites only his three-page 1997 editorial on RESERPINE. (Schaefer Dec., Exhibit 14.) That article has a two-paragraph section that discusses akathisia. This apparently constitutes his "extensive" writings on the topic.

Dr. Healy states that there is a "consensus that [akathisia] can be linked to both suicide and violence." But Dr. Healy fails to present evidence that any persons among those identified in all of the clinical trials reported to FDA, both pediatric and adult, who reported suicidal thoughts or acts, or attempted suicide while taking study medication, experienced akathisia. For instance, Dr. Healy did not review patient narratives for suicidality-related adverse events in

40 Dorland's Illustrated Medical Dictionary, 28th ed. (1994).

Forest's submissions to FDA. (Schaefer Dec., Exhibit 5, Healy Dep., p. 70.) He speculates that some persons taking SSRIs become akathisic, and that some persons with akathisia become suicidal, therefore, some persons taking SSRIs will become suicidal. Any support for this is anecdotal at best. There is no reliable scientific evidence offered by Dr. Healy that SSRI-induced akathisia causes suicide.

2. Emotional Blunting

Dr. Healy's claims that SSRIs can produce "emotional blunting" and "an abnormal absence of fear." He claims that persons in this state can act without fear of consequence. He does not mention suicide, suicidality, CELEXA or LEXAPRO here. He does not claim that there is any evidence to support an association between "emotional blunting" and suicide. He doesn't state an opinion that there is such an association.

At deposition, Dr. Healy was shown a 2004 article regarding 30 elderly, healthy volunteers given SSRI antidepressants.[41] This article, titled "SSRIs Do Not Cause Affective Blunting in Healthy Elderly Volunteers" reported no suicidality-related adverse events among the participants. The authors concluded that SSRIs are not associated with affective blunting. But, as Dr. Healy admitted, the study found among those healthy volunteers taking SSRIs that they were less troubled by "bad things" happening. (Schaefer Dec., Exhibit 5, Healy Dep., p. 309.) This paper actually cited Dr. Healy's 2000 publication of his 20-person study conducted in 1997, and came to contrary conclusions. Dr. Healy was unaware of it. (Schaefer Dec., Exhibit 5, Healy Dep., pp. 306-307.) He admitted the article could have been found relatively easily. (Schaefer Dec., Exhibit 5, Healy Dep., p. 307.)

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[41] Patricia M. Furlan, et al., "SSRIs Do Not Cause Affective Blunting in Healthy Elderly Volunteers," AM J Geriatr Psychiatry 2004; 12: 323-330. (Schaefer Dec., Exhibit 28.)

3. Psychotic Decompensation

Dr. Healy claims that all SSRIs he has reviewed cause psychotic decompensation. He claims that up to 8% of persons admitted to psychiatric facilities may suffer from mania or psychosis induced by SSRI antidepressants. Finally, he claims that there is a well-known link between psychosis and suicide. (Schaefer Dec., Exhibit 4, Healy Report, p. 35.)

As support for his claim that SSRIs such as CELEXA and LEXAPRO cause psychosis, Dr. Healy claims that he has access to unpublished, non-peer-reviewed data that shows psychotic decompensation occurring "at a higher rate with SSRIs than occurs on placebo." (*Id.*) As he reveals nothing more about this data, it cannot be tested or evaluated to determine whether it is reliable.

Dr. Healy also cites a 2001 journal article in support of his claim that SSRIs induce as much as 8% of the mania and psychosis suffered by persons admitted to psychiatric facilities. (*Id.*) This study, however, simply analyzed 533 consecutive psychotic patient admissions to a psychiatric hospital, and found that about 8% had taken antidepressants.[42] This was not a controlled trial or an epidemiology study. There was no placebo control. There was no baseline or comparison population. Moreover, none of the psychotic patients was taking LEXAPRO or CELEXA. Dr. Healy even admitted, "I think you have to be careful drawing conclusion[sic] from the study." (Schaefer Dec., Exhibit 5, Healy Dep., p. 310.) Accordingly, Dr. Healy has no basis to conclude that CELEXA and LEXAPRO cause psychotic decompensation.

4. Other Proposed Mechanisms

Dr. Healy's method of using a flawed mechanistic chain-of-causation logic as "evidence for General Causation" could be extended to examples like these:

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[42] Adrian Preda, et al., "Antidepressant-Associated Mania and Psychosis Resulting in Psychiatric Admissions," J Clin Psychiatry 2001; 62: 30-33. (Schaefer Dec., Exhibit 29.)

Some persons who use antidepressants sleep walk. Persons who sleep walk have been known to commit violent acts. In this way, CELEXA/LEXAPRO can cause persons to commit violent acts, including suicide.

Some persons who use SSRIs become alcoholic. Persons who are alcoholic may become suicidal. In this way, CELEXA/LEXAPRO can cause suicide.

Some persons who use SSRI antidepressants have delayed ejaculation. Persons practicing autoerotic asphyxiation and taking SSRIs may kill themselves by protracted asphyxiation if ejaculation is delayed. Therefore, CELEXA/LEXAPRO can cause suicide.

Persons using SSRI antidepressants can have difficulty urinating. Persons who have difficulty urinating can become overwrought by this and become suicidal. Therefore, CELEXA/LEXAPRO can cause suicide.

One could understandably react to those as ridiculous and absurd suggestions in support of a causal relationship between antidepressants and suicide. However, each of those scenarios was stated during the sworn testimony of Dr. Healy as his examples of mechanisms not disclosed in his report, but on which he may rely. (Schaefer Dec., Exhibit 5, Healy Dep., pp. 284-294.)

Review of Dr. Healy's report and his testimony at deposition shows that his recitation of proposed mechanisms of "suicide induction" lack reliable support and are speculative. These purported mechanisms linking akathisia, psychotic decompensation, emotional blunting (and his other examples) with SSRI use and suicide are not reliable "evidence for General Causation." Opinions based upon a methodology that relies upon such purported mechanisms of "suicide induction" as evidence of a causal relationship, in the absence of an established association between CELEXA, LEXAPRO, and suicide, is untrustworthy.

E. Dr. Healy's allegations about what he believes to be the prevalence of so-called "ghost writing" of journal articles by the pharmaceutical industry is wholly irrelevant and no support for his opinions that CELEXA and LEXAPRO cause suicide, particularly in view of the fact that Dr. Healy made no inquiry regarding Forest or any publications dealing with CELEXA or LEXAPRO.

The fifth component of Dr. Healy's "evidence of General Causation" is entitled "5/False Scientific Consensus." It begins at page 36 of his report. In the two pages that follow, Dr. Healy claims that it is "abundantly clear" that clinical studies conducted by or for drug companies are often unpublished, or incomplete if published. He claims that drug companies "get the results they pay for." He claims that articles are "ghost written" by drug companies and contain "important commercial messages." (Schaefer Dec., Exhibit 4, Healy Report, pp. 36-37.)

Those practices are so pervasive, according to Dr. Healy, that "[t]here is in all probability not a single article in the field claiming there is no problem in this group of drugs that is not authored by someone who is not in receipt of company funding or other support." (Schaefer Dec., Exhibit , Healy Report, p. 37.) Dr. Healy gives his advice to the Court regarding evidence Forest submits in its defense:

> Thus the Court in adjudicating on LEXAPRO/CELEXA has to consider that a large portion of company defense which is portrayed as science based has actually been put together by the companies, commandeering the appearances of science, without having any basis in independent science.

(*Id.*)

This section of Dr. Healy's report provides no specifics concerning Forest studies. There is no disclosure of what Dr. Healy believes to be relevant to the question whether CELEXA and LEXAPRO cause suicide. Like Dr. Healy's lengthy and irrelevant discussion of the relative efficacy of escitalopram versus citalopram discussed above, there is no mention of suicide or suicidality in this portion of Dr. Healy's report. As a result it is not possible to identify what evidence Dr. Healy is trying to warn the Court about in terms of CELEXA and LEXAPRO.

There is no way to determine whether or how his general accusations about the drug industry have any relevance to the evidence in this case.

At deposition, Dr. Healy was asked about his assertion that practices he was critical of, such as so-called "ghost writing" by drug company authors, were the "norm" and involved Forest in addition to other drug companies. In particular, he was asked whether his method in arriving at this conclusion was to impute conduct at another company to Forest:

Q. [P]art of what you're doing is generalizing what you understand other companies do to Forest - - Without direct proof of Forest engaging in those behaviors?

Dr. Healy: Part of what I'm doing is that, yes.

(Schaefer Dec., Exhibit 5, Healy Dep. p. 54.)

Dr. Healy asserts, in typical doublespeak, that it is Forest's burden to prove him wrong in his assumptions:

> I would be awfully keen to see any evidence from any of the companies that haven't engaged in a number of the practices that most of the people that I've been aware of from all of the companies that I've had dealings with have said are industry norms.

(Schaefer Dec., Exhibit 2, Healy Dep., p. 53.)

Dr. Healy claims that it is "highly likely that pretty well all of the articles, both CELEXA and LEXAPRO, are ghost written" and "it would not make sense for a person like me to specifically examine the articles on either CELEXA or LEXAPRO and to try to determine if those were ghost written or not." (Schaefer Dec., Exhibit 2, Healy Dep., p. 56-57.) Dr. Healy was asked about the method of relying upon such assumptions as evidence in support of his opinions:

Q. Is it good science to you, Dr. Healy, to – to generalize from either one compound to another or conduct of one company to another without having specific facts to support it? Is that good science to you?

Dr. Healy: Yes, it is.

Far from good science, it is not scientific at all. It is not a reliable methodology that should be allowed to support the admissibility of Dr. Healy's opinions. Dr. Healy's method of finding fault with conduct that he claims is a "norm" in the drug industry, and assuming that Forest has engaged in such conduct as "evidence or General Causation" is nothing more than irrelevant and inadmissible *ipse dixit*. *See Arnold v. Amada North America, Inc.*, 77 Fed. R. Evid Serv. 248, 2008 WL 2411789 (E.D. Mo. 2008).

This whole section of Dr. Healy's "evidence of General Causation" fails the basic test of relevance under Rule 702. Dr. Healy fails to connect his unfounded assumptions and pure speculation about Forest's conduct regarding "ghost writing" to facts at issue here. See *Lauzon v. Senco Products, Inc.*, 270 F.3d 681, 688 (8th Cir. 2001). Dr. Healy offers no explanation how the issue of "ghost writing" pertains to evidence whether CELEXA and LEXAPRO cause suicide. Dr. Healy's warning to the Court that Forest's defense will lack "any basis in independent science" (Schaefer Dec., Exhibit 4, Healy Report, p. 37) is an insulting broadside directed against Forest, but his cannons are shooting blanks. Nowhere in his report or at his deposition has Dr. Healy provided any evidence that Forest engaged in conduct Dr. Healy alleges to be responsible for a purported "false scientific consensus" involving the issues of CELEXA, LEXAPRO and suicide.

F. Dr. Healy's failure to address a large body of contrary epidemiological data and research is fatal to his reliability

Since Dr. Healy was excluded in *Miller* a decade ago, the volume of epidemiologic research and data that shows no link between antidepressants and suicide in adults has grown significantly. Important peer-reviewed studies and exhaustive FDA research *have* shown a link

between antidepressants and suicide in adults, *but it is the existence of a protective effect*.[43] Contrary to accepted scientific principles, Dr. Healy ignores these results.

The REFERENCE MANUAL states:

> [A]n expert who seeks to testify about the findings of epidemiological studies must be knowledgeable about the results of the studies and must take into account those studies that reach conclusions contrary to the position the expert seeks to advocate.[44]

And in a case involving nearly identical allegations (adult murder-suicide allegedly induced by an antidepressant) and plaintiffs' lead trial counsel in this litigation, the District Court in New Mexico found that flaw fatal. That court excluded plaintiffs' expert, Grace Jackson, M.D., from testifying that Prozac can cause an adult to commit suicide or murder. The court's explanation of the significance of epidemiological data in the general causation analysis, and the consequences of failing to address contrary data, are instructive:

> Epidemiological studies are the best evidence of causation in a case such as this, in which exposure to a substance is alleged to have caused injury. [Citations omitted.] In attempting to prove that exposure to a substance caused an injury, "a 'lack of epidemiologic studies supporting [a plaintiff's] claim creates a high bar for [a plaintiff] to surmount with respect to the reliability requirement." [Citations omitted.] A controlled clinical study, a type of epidemiological study in which one group of subjects is exposed to the agent of interest and the other group is not exposed, "is considered the gold standard for determining the relationship of an agent to a disease or health outcome." *Reference Manual on Scientific Evidence* at 338 (Federal Judicial Education Center 2d ed. 2000).
>
> Dr. Jackson's report does not contain any citation to any controlled clinical trial or other epidemiological study which demonstrates that the ingestion of Prozac creates an increased risk or an increased incidence of the following conditions: akathisia, suicidal thinking, suicidal behavior or completed suicide, violence or homicidal behavior, worsening depression, psychotic decompensation, psychiatric rage, impulsivity or impulsive

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43 *See* Schaefer Dec., Exhibits 1, 11, 12, 13.

44 Margaret A. Berger, "The Admissibility of Expert Testimony," REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 3d 23 (West 2011).

> behavior, or disinhibition or diminished capacity to resist engaging in homicidal or suicidal behavior. Nor did she rely on any such studies, to the extent any existed, in forming her opinion. [Citations omitted.]
>
> **Even more damaging to Dr. Jackson's reliability than her lack of reliance on epidemiological studies to generate and support her conclusions is her failure to grapple with any of the myriad epidemiological studies that refute her conclusion.**
>
> . . .
>
> There are numerous peer-reviewed publications on controlled clinical trials, meta-analyses of controlled clinical trials, and other epidemiological studies that support the proposition that Prozac and other SSRIs are not associated with suicidality or violent, aggressive behavior. [Citations omitted.]
>
> The Tenth Circuit made clear its view of the value of epidemiological studies in *Norris*, stating that "where there is a large body of contrary epidemiological evidence, it is necessary to at least address it with evidence that is based on medically reliable and scientifically valid methodology." [Citations omitted.] The *Norris* court went on to hold that **"[w]hile the presence of epidemiology does not necessarily end the inquiry, where epidemiology is available, it cannot be ignored. As the best evidence of general causation, it must be addressed." *Id.* Fatally for her reliability, rather than accounting for any of the many contrary epidemiological studies that showed no medically reliable link between Prozac and homicide/suicide in the target population in reaching her conclusion or writing her report, Dr. Jackson did not address them or discounted them without explanation. As a consequence, the methodology she used to reach her conclusion is ultimately unreliable,** as "[n]on-epidemiological studies, singly or in combination, are not capable of proving causation in human beings in the face of an overwhelming body of contradictory epidemiology evidence." [Citations omitted.]

(Schaefer Dec., Exhibit 27, pp. 25-28.)

As Dr. Jackson failed to do in *Rimbert*, Dr. Healy here fails to address the "myriad epidemiological studies that refute [his] conclusion." *See Rimbert* at p. 26. Since the *Rimbert* court tackled these issues, additional persuasive evidence contrary to Dr. Healy's opinions has

been published.[45] Dr. Healy completely – and improperly – ignores or dismisses that evidence with no reasoned basis, claiming what amounts to a conspiracy theory as support for his approach.

II. CONCLUSION

David Healy concluded long before his report and testimony here that antidepressants, particularly SSRI antidepressants, cause suicide. His methodology and purported evidentiary support were exposed as unreliable in 2002. His testimony was properly excluded in a detailed and well-reasoned decision that was affirmed in 2004 by the Tenth Circuit Court of Appeals. Unless something dramatically changed in his approach, that should have been the end of Dr. Healy on the subject of antidepressants and suicide in United States courts.

As shown here, Dr. Healy's methods, opinions, and conclusions have not changed since being excluded in *Miller*. They are, in fact, even less trustworthy as offered here than they were in the *Miller* case. In the intervening decade since his testimony was excluded by the *Miller* court, much has occurred that further shines light on Dr. Healy's flawed and improper methodology and proffered testimony. But rather than scientifically and objectively investigating the state of the science as it has progressed, Dr. Healy turns a blind eye.

Dr. Healy manipulates data from other researchers and creates misleading "evidence" of associations that he has not subjected to peer review. He cherry picks from or chooses not to review the available evidence. He attempts to support his assumptions and "distinct minority" opinions by employing the method of claiming that pervasive industry and medical collusion have so compromised the field that it is, except for his own contributions, *prima facie* flawed. Having looked for no evidence regarding Forest, his defense is "no one has shown me there is none." Whole sections of his report have no relevance to Forest, or whether CELEXA and

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[45] *See* Schaefer Dec., Exhibits 1, 11, 12, 13.

LEXAPRO cause suicide. Dr. Healy's opinions and innuendos may make for entertaining reading and lecture hall drama, such as when telling an audience to "forget the science"[46] but they are quackery, not reliable scientific methodology. Dr. Healy should be excluded. A proposed order is attached hereto as Exhibit 1.

Respectfully submitted,

Dated: October 12, 2012

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46 In lecturing to a support group in New Zealand in September 2011, Dr. Healy's attitude and approach were well summarized by the suggestions he gave to the attendees:

> "What this talk has been all about is getting you to believe the evidence of your own eyes. **Forget the science. Forget the controlled trials . . . .** [W]hen you've got a lot of people here in the room exposed to the same thing, you're all coming to the same conclusion, there comes a point where you have to go with that."

(Schaefer Dec., Exhibit 5, Healy Dep., pp. 282-284.) (emphasis added) Presentation to CASPER, 1hour, 15 minutes, 08 seconds at http://www.youtube.com/watch?v=5bu1uApqIr4.

CERTIFICATE OF SERVICE

I hereby certify that a true and accurate copy of the foregoing Defendants' Memorandum in Support of Defendants' Motion to Exclude Testimony of Plaintiffs' Expert, David Healy, MD, was filed and served electronically this 12th day of October, 2012, upon attorneys who have completed ECF registration as required by the Court.

/s/ *John R. Ipsaro, Esq.*
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